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(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : WEIR, Niall, Galbraith [GB/GB]; CHANDLER, Malcolm [GB/GB]; BAMFORD, Mark, James [GB/GB]; Glaxo Group Research Limited, Greenford Road, Greenford, Middlesex UB6 0HE (GB).

(74) Agents: BREWER, Christopher, Laurence et al.; Glaxo Holdings p.l.c., Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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(54) Title: SYNTHESIS OF N-ACETYL NEURAMINIC ACID DERIVATIVES

(57) Abstract

A method for the preparation of 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-eno-pyranosonic acid which comprises amination of 5-acetamido-4-cyanoamide-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid.

INTERNATIONAL SEARCH REPORT

information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9116320	31-10-91	AU-A- 7533891	12-12-91
		AU-A- 7759091	11-11-91
		CN-A- 1057260	25-12-91
		EP-A- 0526543	10-02-93
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SYNTHESIS OF N-ACETYL NEURAMINIC ACID DERIVATIVES

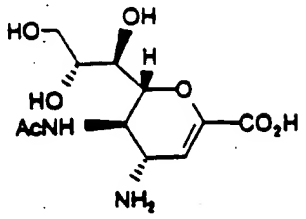
The present invention relates to a process for the preparation of derivatives of N-acetyl neuraminic acid. More particularly the invention relates to a process for the preparation of 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid (the 4-guanidino analogue of DANA; also known as 5-(acetylamino)-2,6 anhydro-3,4,5-trideoxy-4-guanidino-D-glycero-D-galacto-non-2-enonic acid) and derivatives thereof.

PCT/AU91/00161 (publication no. WO91/16320) describes a number of derivatives of 5-acetamido-2,3,5-trideoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (2,3-dideoxy-2,3-didehydro-N-acetyl-neuraminic acid; DANA) including the 4-guanidino analogue of DANA. The 4-guanidino analogue of DANA is prepared by the reaction of the corresponding O-acyl protected 4-amino analogue of DANA by reaction with S-methylisourea followed by deprotection.

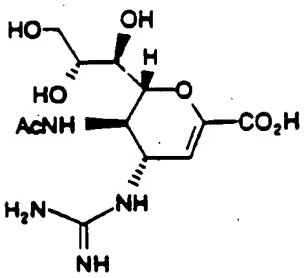
We have now found an improved method of preparing the 4-guanidino analogue of DANA .

The invention thus provides in a first aspect a method for the preparation of 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-eno-pyranosonic acid which comprises amination of 5-acetamido-4-cyanoamide-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (the 4-cyanoamide analogue of DANA, also known as the 4-cyanamido analogue of DANA).

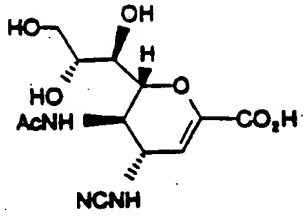
The structure of the 4-amino, 4-cyanoamide and and 4-guanidino analogues of DANA are shown below:



4-amino analogue of DANA



4-guanidino analogue of DANA



4-cyanoamide analogue of DANA

The amination may be effected by any suitable source of ammonia for example gaseous ammonia, liquid ammonia or aqueous ammonia. Preferably aqueous ammonia eg 0.880sg ammonia is used.

The reaction may be carried at elevated temperature, for example from about 50°C to 100°C. Conveniently the reaction is carried out at reflux when aqueous ammonia is employed.

The molar ratio of the 4-cyanoamide analogue of DANA to the source of ammonia employed in the reaction may be from about 1:50 to about 1:250 for example about 1:100.

A buffer is preferably employed in the reaction. Any suitable buffer may be employed for example ammonium salts such as ammonium formate or ammonium

acetate and alkali metal salts - preferably the buffer is employed in a molar excess of about 5 to 7, for example 6, fold.

The desired 4-guanidino analogue of DANA may be isolated by any conventional method from the reaction mixture, for example by crystallisation or chromatography. In particular the 4-guanidino analogue of DANA may be isolated by treatment of an aqueous solution with an organic solvent in which the compound is insoluble. Such solvents include for example *iso*propyl alcohol (IPA) and acetone.

The 4-cyanoamide analogue of DANA may be prepared from the corresponding 4-amino analogue of DANA by reaction with a source of electrophilic cyanide. Preferably a cyanogen halide, for example cyanogen bromide, is employed as the source of cyanide.

The preparation of the 4-cyanoamide analogue of DANA is preferably carried out in a protic, non-aqueous solvent for example a lower aliphatic alcohol such as ethanol or, preferably, methanol conveniently in the presence of a buffer such as sodium acetate.

The reaction is conveniently carried out at ambient temperature.

The 4-cyanoamide analogue of DANA is a novel compound and forms a further aspect of the invention.

The 4-amino analogue of DANA is a known compound (International Application Publication No WO91/16320)

The present invention is further described by the following examples which are for illustrative purposes only and should not be construed as a limitation of the invention.

Example 1

(i) 5-Acetamido-4-amino-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (3g,10.35mmol) was treated with cyanogen bromide (1.1 eq) in dry methanol in the presence of sodium acetate (2.2 eq) for 2 days at 21°C . The

reaction mixture was then treated with methanol: propan-2-ol (1:1 260ml) to precipitate out the desired 5-acetamido-4-cyanoamide-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid .

(ii) The product of step (i) (1g, 3.17mmol) was reacted in the presence of ammonium formate (6 eq) with 0.880 sg ammonia (20ml) at 88°C for 4hrs. The product was purified by chromatography on ion-exchange resin (Dowex 50W x8 (H^+)15ml, eluted with 0.6M triethylamine) followed by crystallisation from water/propan-2-ol (8:20) to give 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid (220mg) identical with authentic product.

Claims

1. A method for the preparation of 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-eno-pyranosonic acid which comprises amination of 5-acetamido-4-cyanoamide-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid.

2. A method as claimed in claim 1wherein the amination is effected with gaseous ammonia, liquid ammonia or aqueous ammonia.

3. A method as claimed in claim 1 or claim 2 wherein the amination is effected with aqueous ammonia.

4. A method as claimed in any one of claims 1 to 3 wherein the amination is effected with 0.880sg ammonia.

5. A method as claimed in any one of claims 1 to 4 wherein the molar ratio of 5-acetamido-4-cyanoamide-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid to ammonia is from about 1:50 to 1:250.

6. A method as claimed in any one of claims 1 to 5 wherein the molar ratio of 5-acetamido-4-cyanoamide-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid to ammonia is about 1:100.

7. A method as claimed in any one of claims 1 to 6 wherein the reaction is carried out at a temperature of from about 50-100°C.

8. A method as claimed in any one of claims 1 to 7 wherein the reaction is carried out in the presence of a buffer.

9. A method as claimed in any one of claims 1 to 8 wherein the reaction is carried out in the presence of a buffer selected from an ammonium salt or an alkali metal salt.

10. 5-Acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-eno-

pyranosonic acid whenever prepared by the method of any one of claims 1 to 9.

11. 5-Acetamido-4-cyanoamide-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 93/02574

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D309/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LIEBIGS ANNALEN DER CHEMIE vol. 1991, no. 2 , February 1991 , WEINHEIM pages 129 - 134 ERWIN SCHREINER ET. AL. *Article*	1-11
A	WO,A,91 16320 (BIOTA SCIENTIFIC MANAGEMENT PTY) 31 October 1991 cited in the application *Document*	1-11
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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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